IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Clarence N. Ahlem, et al.
App. No.	: 10/602,330
Filed	: June 23, 2003
Title	: Pharmaceutical Compositions and Treatment Methods
Examiner	: Barbara P. Badio
Group Art Unit	: 1617
Confirmation No.	: 9052
Customer No.	: 26551
Docket No.	: 202.2D2

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Box AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicants submit this paper by electronic submission in response to the final office action that the Office mailed on May 18, 2007. Applicants hereby request a pre-appeal brief review of the final rejection in the above-identified application.

Applicants are filing no amendments with this request.

Applicants file this request with a notice of appeal and the required notice of appeal fee.

Applicants request this review for the reasons stated, which begin on page 2.

The undersigned is the attorney of record (reg. No. 36,616).

35 USC § 102(a). Examiner Badio rejected claims 119, 130, 139 and 141 of the present patent application as allegedly anticipated in view of U.S. patent 5,461,042 (hereafter the " '042 patent", of record) or 5,387,583 (hereafter the " '583 patent", newly cited by Examiner Badio). Applicants respectfully traverse this rejection because the cited patents do not expressly or inherently anticipate any of the rejected claims. The law that defines the nature of what is required for a reference to anticipate a claim is clear and settled. Specifically, "invalidity by anticipation requires that the four corners of a single, prior art document describe every element of the claimed invention. *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000)", cited by *Xerox Corp. v. 3Com Corp.*, 458 F.3d 1310 (Fed. Cir. 2006). For inherent anticipation, the court has stated: "Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claims limitations, it anticipates. (quoting *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999)." *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 77 U.S.P.Q.2D 1321 (Fed. Cir. 2005).

Claims 119 and 130 recite administration to a human by one of three specified parenteral routes of administration of a dose of the compound androst-5-ene-3β,17β-diol (referred to as "AED" or "βAED" in the cited patents and hereafter) sufficient to generate a neutrophil response in a human. The teaching at column 17, lines 38-41 in the '042 patent specifies a dose range of 0.2 to 30 mg/day as suitable for "larger adult mammals", with a lower dose needed for administration by several specified parenteral routes, e.g., subcutaneous injection. The evidence of record shows that this dose range would not be expected to elicit a detectable neutrophil response in humans (declaration submitted February 21, 2007, of record). The other portions of the '042 patent that Examiner Badio cites do not specify any dose that would necessarily elicit a neutrophil response in humans, particularly in view of the express teaching to use the specified dose range for "larger adult mammals" when administered by parenteral routes would require an even lower AED dose than the maximum 30 mg dose. The only express teaching about a specific dosage for AED in the '583 patent is similar to what the '042 patent teaches, i.e., a capsule containing 15 mg of AED for oral use is taken once or twice per day (col. 19, line 65 through col. 20, line 2). Examiner Badio points to col. 3, lines 31-62 as somehow disclosing a dosage of AED that would necessarily elicit a neutrophil response in a human or a non-human primate. Applicants respectfully disagree and they note, this portion of the '583 patent discloses no specific dosage for

AED. In view of this, there is no express or inherent teaching of a dose in the '583 patent that would necessarily elicit a neutrophil response in humans.

Claims 139 and 141 recite treatment of a non-human primate, but neither cited patent describes any non-human primate. Therefore, the rejection of claims 139 and 141 cannot be sustained because both references lack this claim element. Because neither cited reference expressly or implicitly anticipates any of claims 119, 130, 139 and 141 Applicants respectfully request withdrawal of the rejection under 35 USC § 102(a).

35 USC § 103(a). Examiner Badio rejected claims 119-146 as allegedly obvious in view of U.S. patent 5,461,042 (of record) or 5,387,583 (of record) in view of Carr (*J. Neuroimmunology*, 1998). Applicants respectfully traverse the rejection as clear example of a rejection based on hindsight, which is improper. *KSR Int'l. Co. v. Teleflex Inc.*, 550 U.S. __ (2007); *In re Dembiczak*, 175 F.3d 994 (Fed. Cir. 1999). As discussed below, Examiner Badio has not established a *prima facie* case of obviousness and the rejection should be withdrawn. Examiner Badio did not provide a complete citation for, or a copy of, the Carr reference. Applicants presume that the Carr publication is D.J.J. Carr, *J. Neuroimmunol.*, 89:160-167, 1998 and comments below are based on this citation.

The claims in this application recite methods to treat innate immune suppression in humans or non-human primates by administering AED to elicit a neutrophil response. Neither the '042 nor the '583 patent teaches or suggests the claimed treatment methods when combined with Carr, none of which mention neutrophils. Examiner Badio states at page 3 of the office action that Carr "teaches the immunomodulatory effect of androstenediol and subcutaneous administration of 32-320 mg/kg (see entire article, especially Abstract and Discussion)." Although Examiner Badio asserts that these dosages were effective, this is incorrect. Carr states in the abstract: "lower doses (32.0-100.0 mg/kg) were without effect." Clearly, Examiner Badio has misunderstood and misapplied this reference. Efficacy in the Carr protocol required a subcutaneous 320 mg/kg dose, which would amount to subcutaneously injecting a 22.4 g dose into a 70 kg adult human or 1.9 g into a 6 kg adult rhesus monkey. A subcutaneous 22.4 g dose is not feasible for humans and a 1.9 g dose is well above what one of ordinary skill in the art would contemplate for a non-human primate. The effective dose in Carr is far above the doses that claims 121, 123-124, 126-129, 132-138 and 146 recite for humans or non-human primates. In view of the fact that Examiner Badio has misunderstood and misapplied Carr, the rejection is improper.

Examiner Badio asserts that examples 1-5 in the '583 patent are relevant to the obviousness analysis. Applicants submit that they are either irrelevant or are evidence of non-obviousness for the claimed methods. In example 1, AED did not affect cell proliferation in the absence of mitogen (col. 17, lines 1-31). In example 2 AED did not significantly stimulate cell growth compared to control cultures (col. 17, lines 53-58 and col. 18, lines 18-21). Example 3 did not use AED and it is irrelevant. In example 4 AED had essentially no effect on cytokine expression in the presence or absence of hydrocortisone (col. 19, lines 34-35 and 38). Example 5 describes a 15 mg AED capsule for oral administration once or twice per day. Applicants respectfully submit that these examples do not make any of the claimed subject matter obvious when combined with Carr. Applicants see no rationale for combining Carr with the '042 patent or the '583 patent and certainly no rational to suggest lower doses than Carr found to be effective. The rejection is clearly based on hindsight.

A difference between the cited references and the claims relates to the dose regimens that claims 120-128, 131-138 and 142-146 recite. Carr, '042 or '583 alone or together do not suggest any specific dosing regimen and thus these references completely lack this claim limitation. The '042 patent states at col. 17, lines 28-32 that a "preferred method of administration is by subcutaneous injection as a depo. The method is particularly appropriate for administration of the active agents to mammals, since subcutaneous injection is easily performed and the effect is relatively long lasting." There is no teaching in Carr, '042 or '583 that Examiner Badio has described that would teach or suggest the claimed multiple dose protocols. Only hindsight could lead one of ordinary skill in the art to the claimed methods.

At column 17, lines 38-48, the '042 patent expressly teaches a maximum dose of 30 mg for AED for "larger adult mammals" and lower doses for administration by subcutaneous administration or other listed non-oral routes:

> "The dosages used will depend on the size and condition of the host. Test data indicated in this application was obtained in small animals. In larger adult mammals daily dosage of 0.2 to 30 mg/da. of AED is a preferred dosage. . [ ] . . . However, the dosage will vary depending on the route of administration. Subcutaneous, inhalation and intrathecal administration are methods that would require lower dosages of the active agents."

The '042 patent thus expressly teaches AED doses that are too low to achieve the presently claimed biological response in humans or non-human primates. The '042 and

'583 patents are silent about neutrophils and about biological effects of AED actually administered to humans or non-human primates. There was no way that one of ordinary skill in the art could have known that the 15 mg and 30 mg oral AED dosages given in the '042 or '583 patents were too low to elicit a neutrophil response in a human or non-human primate. Given that, there simply was no reason to contemplate the presently claimed subject matter. Only hindsight can make the claimed subject matter obvious because the cited references cannot do so.

At page 4 of the office action, Examiner Badio rejected claims 120-129, 131-138 and 142-146 in view of U.S. patent 5,489,581, col. 11, lines 10-25 and the '042 and/or the '583 patent. Examiner Badio asserts: "the medical art teaches various treatment regimens dependent on patient age, sex, condition etc." Applicants respectfully traverse the rejection. The last sentence of 35 USC § 103(a) states: "Patentability shall not negatived by the manner in which the invention was made." Congress used this language expressly to rebut the reasoning that Examiner Badio tries to assert here. Examiner Badio points to nothing in U.S. 5,489,581 that teaches, suggests or makes obvious any of the presently claimed methods. A listing of a hypothetical dose range of 1-200 mg/kg or 2-50 mg/kg in U.S. 5,489,581 at col. 11, lines 10-12 for a large compound genus coupled with (1) data in the '583 patent showing essentially no efficacy of AED in the spleen cell and cytokine assays and (2) express teaching of a 30 mg oral dose or less in the '042 and '583 patents point to absolutely nothing regarding AED dosages, dose regimens or routes of administration that would elicit a neutrophil response in a human or a non-human primate. The data in Carr showed that for Carr's clinical setting (HSV-1 infection), 32 mg/kg and 100 mg/kg AED dosages were inactive. Given the facts, it is clear that there is no logical basis for expecting dosages or treatment regimens in U.S. 5,489,581 for treating reperfusion injury to apply to treating innate immune suppression. This rejection is based on hindsight.

The record includes evidence of biological efficacy in both non-human primates and in humans. This evidence includes a showing that the treatment with this compound alone increases survival of lethally radiated non-human primates by 20 percentage points compared to placebo treated control animals (declaration submitted February 21, 2007). Applicants believe that this is unprecedented evidence of efficacy, which is objective evidence of non-obviousness. Such evidence must be considered. *Graham v. John Deere Co.*, 383 U.S. 1 (1966). To Applicant's knowledge, no single agent has ever

been shown to increase survival of a non-human primate (or a human) after exposure to a potentially lethal amount of radiation. Radiation exposure is traditionally treated with clinical support including blood transfusions, red cell transfusions and/or antibiotic treatments (e.g., A.M. Farese et al., *J. Clin. Invest.*, 97(9):2145-2151 1996, of record). The present therapy alone without clinical support decreases the severity and/or duration of severe innate immune suppression in part by increasing levels of neutrophils and in part by shortening the period of innate immune suppression by speeding up neutrophil recovery after irradiation.

The record (declaration submitted February 21, 2007) includes evidence that the claimed treatments for humans with the claimed dosages and dose regimens is effective to increase neutrophils in the face of homeostasis mechanisms that tend to keep neutrophil levels constant in the absence of an overt infection or another insult that would trigger a neutrophil increase, e.g., J.E. Layton et al., *Blood*, 74(4):1303-1307, 1989, of record. The increase in neutrophils that are observed in healthy human volunteers was unexpected because it is evidence of efficacy in the face of feedback mechanisms that tend to inhibit a neutrophil response in healthy humans. Evidence of unexpected results for the claimed methods also include the observation that AED elicited a statistically significant neutrophil response in phase I clinical trials (declaration submitted February 21, 2007). Compounds that enter phase I clinical trials rarely have sufficient potency to show efficacy, in situations when this can be done. The biological activity of AED in humans is unexpected and is additional evidence of non-obviousness of the claimed human treatment methods. *Graham v. John Deere Co.*, cited above.

Conclusion. Because this review request is limited to 5 pages of argument, Applicants reserve their right to expand these arguments and to make additional arguments in their appeal brief, if the Office concludes an appeal brief is needed.

In view of the foregoing arguments, Applicants respectfully submit that Examiner Badio has not shown anticipation or obviousness for any claim in view of the record and the cited references.

Applicants request withdrawal of all rejections and allowance of all claims.

Respectfully submitted,

Date: June 6, 2007

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